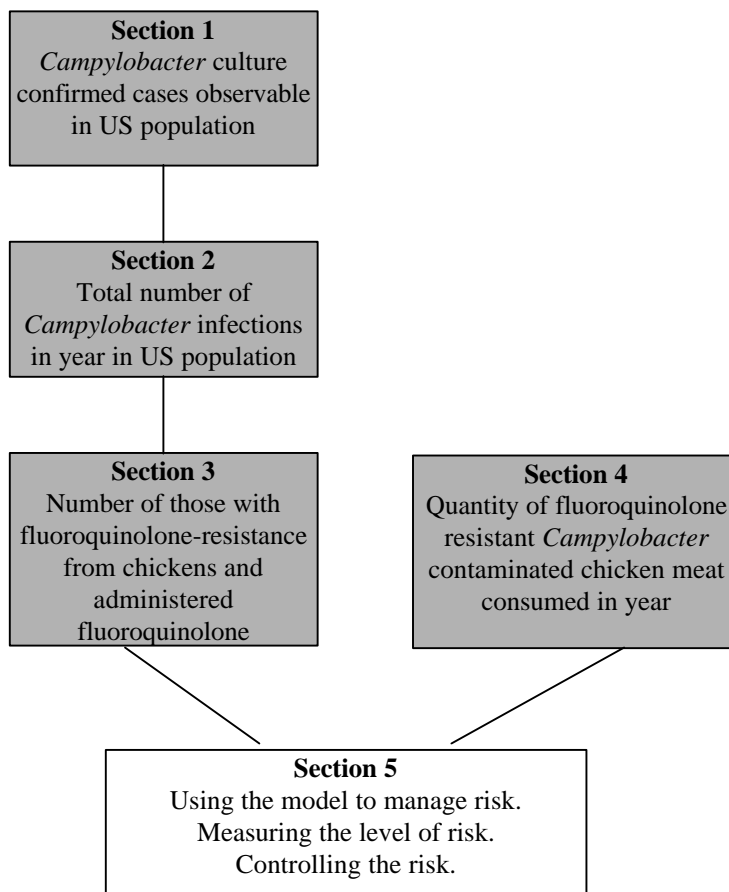


Section 5

**Using the model to manage risk.
Measuring the level of risk.
Controlling the risk.**



Sensitivity analysis

A sensitivity analysis was performed on the risk model to determine which model parameters are contributing the most to the total model outputs' uncertainty. The purpose of this exercise is to determine a) where extra information would be most useful in reducing the uncertainty about a model parameter and thus in the model outputs, and b) the model parameters that the model outputs are most sensitive to and therefore the model and any decisions based on its results are most vulnerable to current lack of knowledge.

Three model outputs were used for the uncertainty analysis: N_{3T} - the total number of human fluoroquinolone resistant infections from domestically reared chicken that sought care in 1998 and were prescribed fluoroquinolone; V_i - the total consumption in 1998 of boneless domestically reared chicken that were contaminated at the slaughter plant with fluoroquinolone resistant *Campylobacter* in US (lbs.); and the ratio N_{3T}/V_i , which provides a good means of comparing the relative uncertainty of the two sides of the risk assessment.

The sensitivity analysis was carried out by fixing each model parameter to the 5th, 25th, 50th, 75th and 95th percentiles of its uncertainty distribution in turn, whilst leaving all other model parameters with their uncertainty distributions. For each percentile, the model is simulated to determine the mean output value. The result is a spider plot (92, 93). The x-axis shows the percentile used for each model parameter and the y-axis shows the magnitude of the mean of the output in question. The degree of influence of an input parameter equates to the range of output mean values corresponding to the input percentiles. For example, eliminating the uncertainty about p_{rh} could potentially move the estimate of N_{3T} to be focused around a value anywhere between 3,300 and 7,000 - a large movement, whereas eliminating the uncertainty about parameter p_b would move the estimate of N_{3T} to be focused somewhere between 4,900 and 5,200 - a small movement.

Sensitivity analysis for N_{3T}

Figure 5.1 illustrates the parameters that contribute the most to the uncertainty in the value for N_{3T} . The parameter p_{rh} produces the greatest vertical range and therefore is the most influential input parameter. The next most important parameters are p_{nc} and p_+ . The parameter p_{rh} plots with a positive gradient so N_{3T} would be larger the true value of p_{rh} . The parameters p_{nc} and p_+ plot with a negative gradient, so the lower their true values, the higher the true value of N_{3T} .

From Figure 5.1 we can conclude that, in order to better estimate the human health impact of fluoroquinolone resistant *Campylobacter* in broilers, it would be useful to first collect more data on (in order of importance):

Proportion of *Campylobacter* infections from chicken that are fluoroquinolone resistant (p_{rh});
Probability that a stool will be requested and submitted from a patient with non-bloody diarrhea (p_{nc}); and
Probability that the culture will confirm *Campylobacter* given tested (p_+).

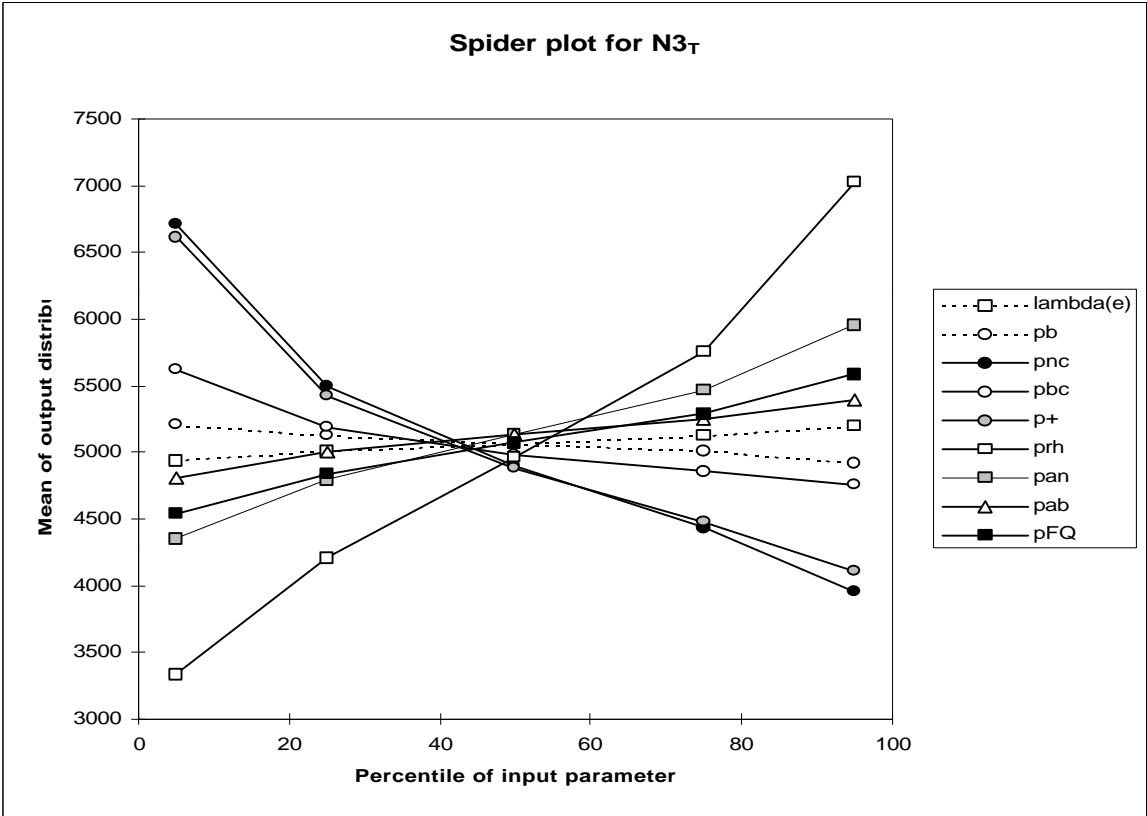


Figure 5.1. The parameters that contribute the most to the uncertainty in the value for N3_T.

Sensitivity analysis for V_i

Figure 5.2 illustrates the parameters that contribute the most to the uncertainty in the value for V_i. There are only two uncertainty parameters in determining this output, p_c and p_{rc}, and p_{rc} (the prevalence of fluoroquinolone resistant *Campylobacter* among *Campylobacter* isolates from slaughter plants) is clearly contributing the greatest uncertainty to the determination of V_i.

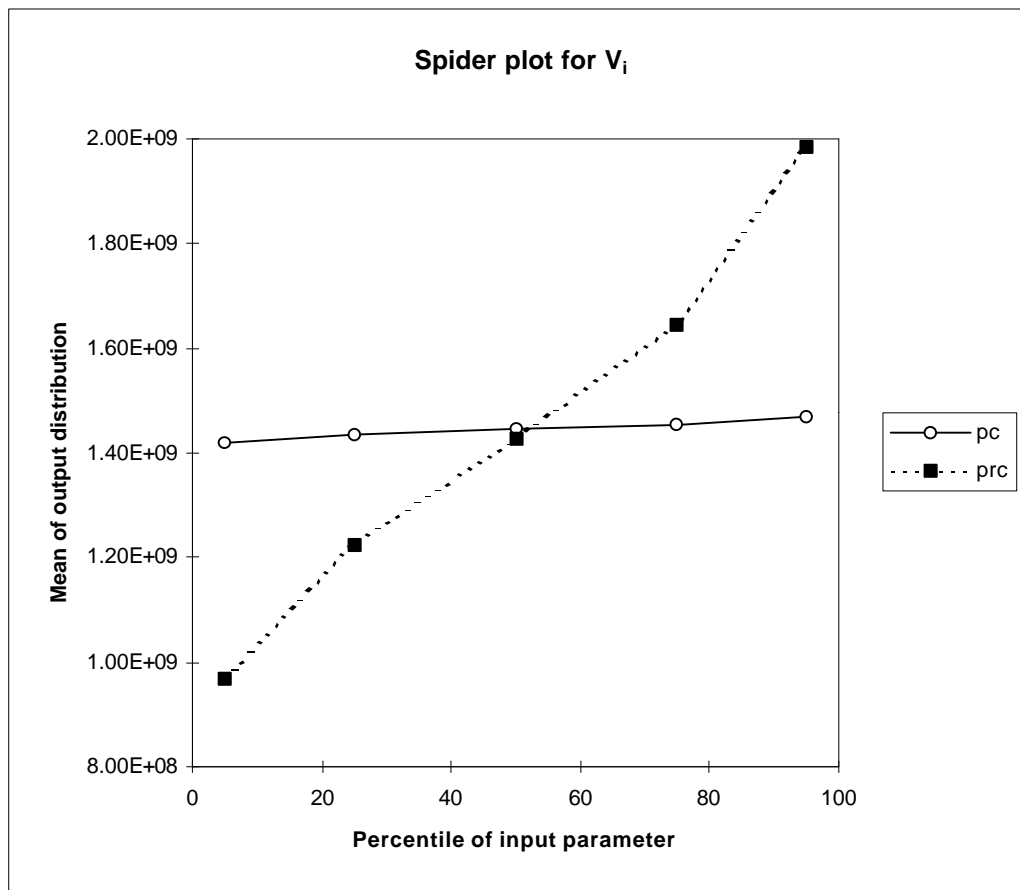


Figure 5.2. The parameters that contribute the most to the uncertainty in the value for V_i .

Sensitivity analysis for $(N3_T/V_i)$

Figure 5.3 illustrates the parameters that contribute the most to the ratio $(N3_T/V_i)$. The parameters p_{rh} and p_{rc} produce the greatest vertical range and therefore are the most influential input parameters. The parameter p_{rc} is the only parameter plotted that contributes to the uncertainty about V_i , i.e. all the other parameters correspond to determining the human health effect which means that we are far more uncertain about the human health side of the problem than the broiler side. This point is further illustrated in Figure 5.4 where percentiles of $N3_T$ and V_i are plotted as inputs to the ratio $(N3_T/V_i)$. Here we can see that there is approximately twice as much uncertainty coming from the human side ($N3_T$) than from the broiler side (V_i).

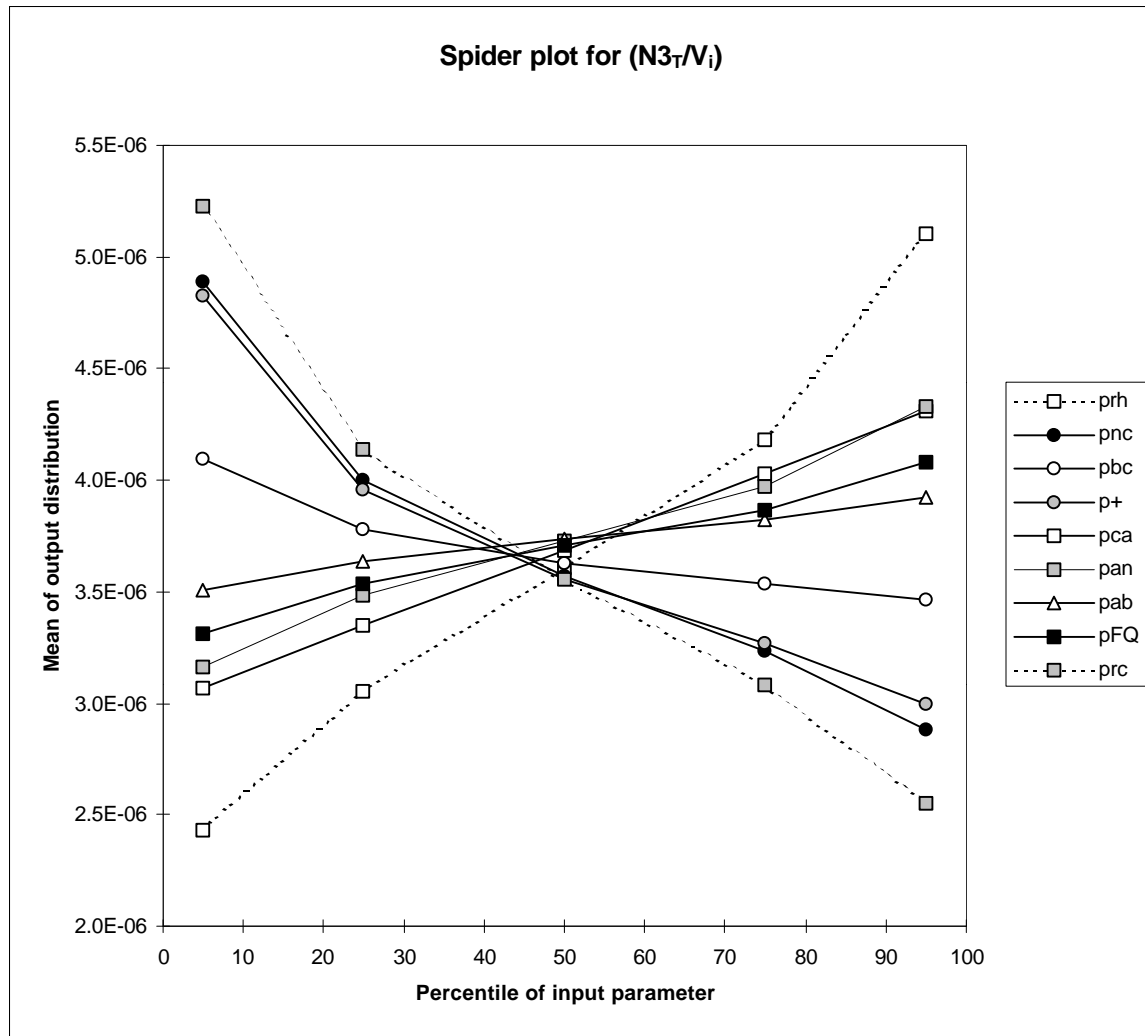


Figure 5.3 The parameters that contribute the most to the ratio (N_{3T}/V_i).

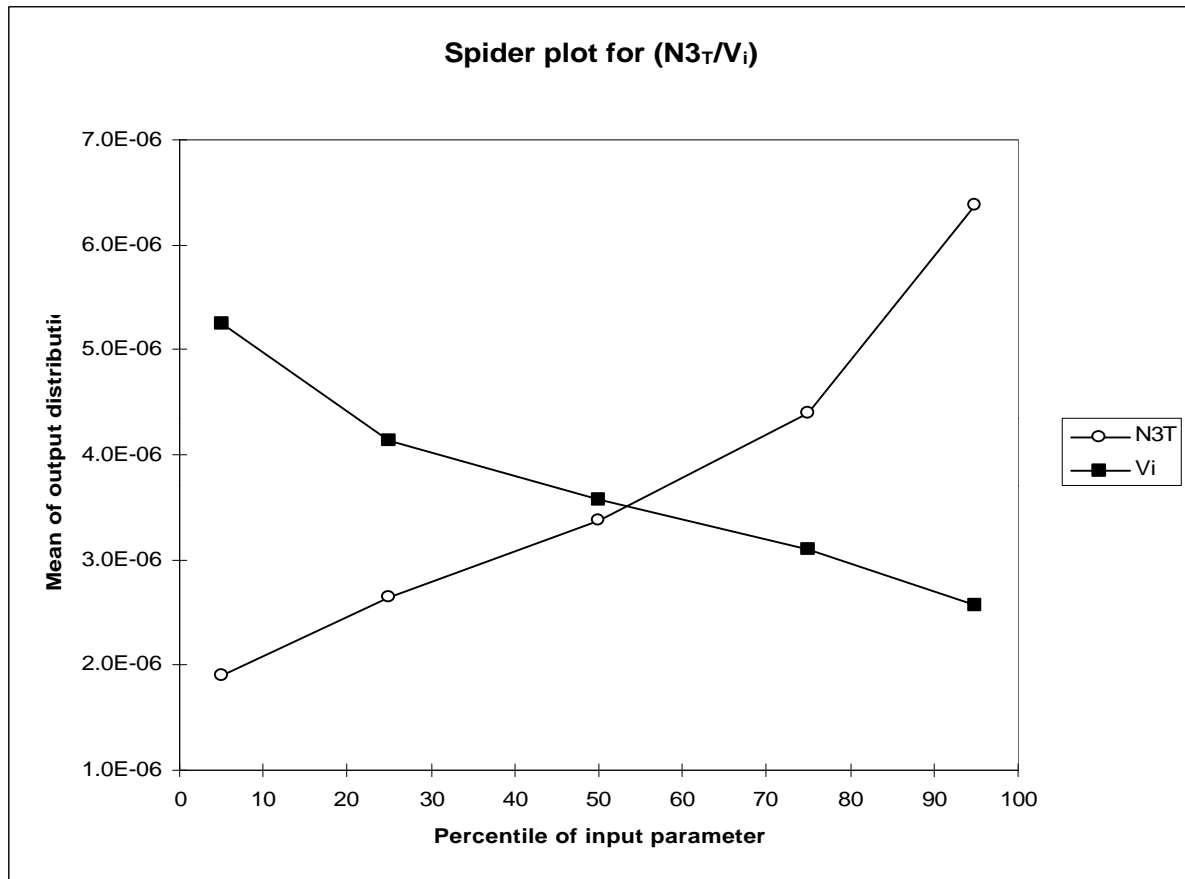


Figure 5.4 Uncertainty from the human side (N_{3T}) compared to the broiler side (V_i).

Sensitivity Analysis Summary

A great deal of information seems to have been collected about the human health impact of fluoroquinolone resistant *Campylobacter* and relatively little seems to have been collected on the fluoroquinolone resistant *Campylobacter* prevalence of broilers, but this analysis shows somewhat surprisingly that the emphasis for further research should first be placed on investigating the human health impact. Further analysis of this model would allow one to determine the increase in knowledge of the risk as a whole by collecting further data points for the uncertainty parameters, which can help ensure that useful data is being collected and in an efficient manner.

Using the model to manage risk

The results and principles of Sections 1 to 4 of this model can be used to measure and monitor the level of risk to the US population posed by fluoroquinolone resistant *Campylobacter* from domestically reared broilers.

Measuring the level of risk

1. Probability

First of all, we can assess the level of risk by calculating the ratio of the number of people who are affected each year N_{3T} to the population at risk. There are various options one may select as the population at risk, shown in the table below:

Table 5.1 Level of Risk Determined for Various Denominators

Denominators	Probability	Equated to 1 in:
US citizen ($=n_{us}$)	0.0019%	61,093
Person with campylobacteriosis ($=N_{2T}$)	0.2265%	521
Person with campylobacteriosis seeking care ($=N_{2en} \cdot p_{nm} + N_{2eb} \cdot p_{bm} + N_{2i}$)	1.739%	63
Person with campylobacteriosis seeking care and prescribed antibiotic ($=N_{2en} \cdot p_{nm} \cdot p_{an} + N_{2eb} \cdot p_{bm} \cdot p_{ab} + N_{2i}$)	3.384%	32

The probability column in this table gives estimates of the probability that an individual randomly chosen from the chosen denominator population at risk in 1998 would have numbered among those for whom fluoroquinolone resistant *Campylobacter* in broilers resulted in a health impact (N_{3T}). The last column offers an alternative expression of the probability as 1 in x that many people find easier to interpret. The table shows mean estimates, but the figures below show the uncertainty around these values.

People will perceive the size of the risk differently in different circumstances. For the average US citizen, the risk may well be perceived presently as being very small: we have estimated that 1 in 61,093 people were affected in 1998, for example. On the other extreme, people with reduced immunity who may be more likely to seek medical help, may perceive the risk as quite significant. The appropriate measure of this risk is vital to determine the appropriate resistance threshold. Four possible denominators are offered for discussion.

The first denominator distributes the risk among the entire US population. The great majority of the US population consumes chicken, and the consumption of a fluoroquinolone resistant *Campylobacter* contaminated chicken product, or consumption of another food item contaminated by chicken (e.g. salad) is a random process. Thus, the great majority of people are exposed to the risk and the randomness of the process means that most people are not in full control of that risk. They may consume the food at a restaurant, other type of food outlet or the home of someone else. Considering only those people in the US population who consume chicken could refine this denominator a little.

The second denominator distributes the risk among people who contract campylobacteriosis from any source. These people will potentially seek medical care and may be prescribed a fluoroquinolone. This denominator puts the risk from fluoroquinolone resistant *Campylobacter* from broilers into context with the total sources of *Campylobacter* infections. Thus, one can make statements like “0.2% of people contracting campylobacteriosis will be affected by the risk”.

The third denominator distributes the risk among those people who contract campylobacteriosis from any source and then seek some medical care. These people are sufficiently ill that they decide they need help. This denominator includes consideration of those people who may be more susceptible to *Campylobacter* than most.

The fourth denominator distributes the risk among those people who contract campylobacteriosis from any source, seek some medical care and are prescribed an antibiotic. Both they themselves and their medical practitioner consider these people sick. The definition represents the group that is most seriously at risk from the failure of fluoroquinolone therapy.

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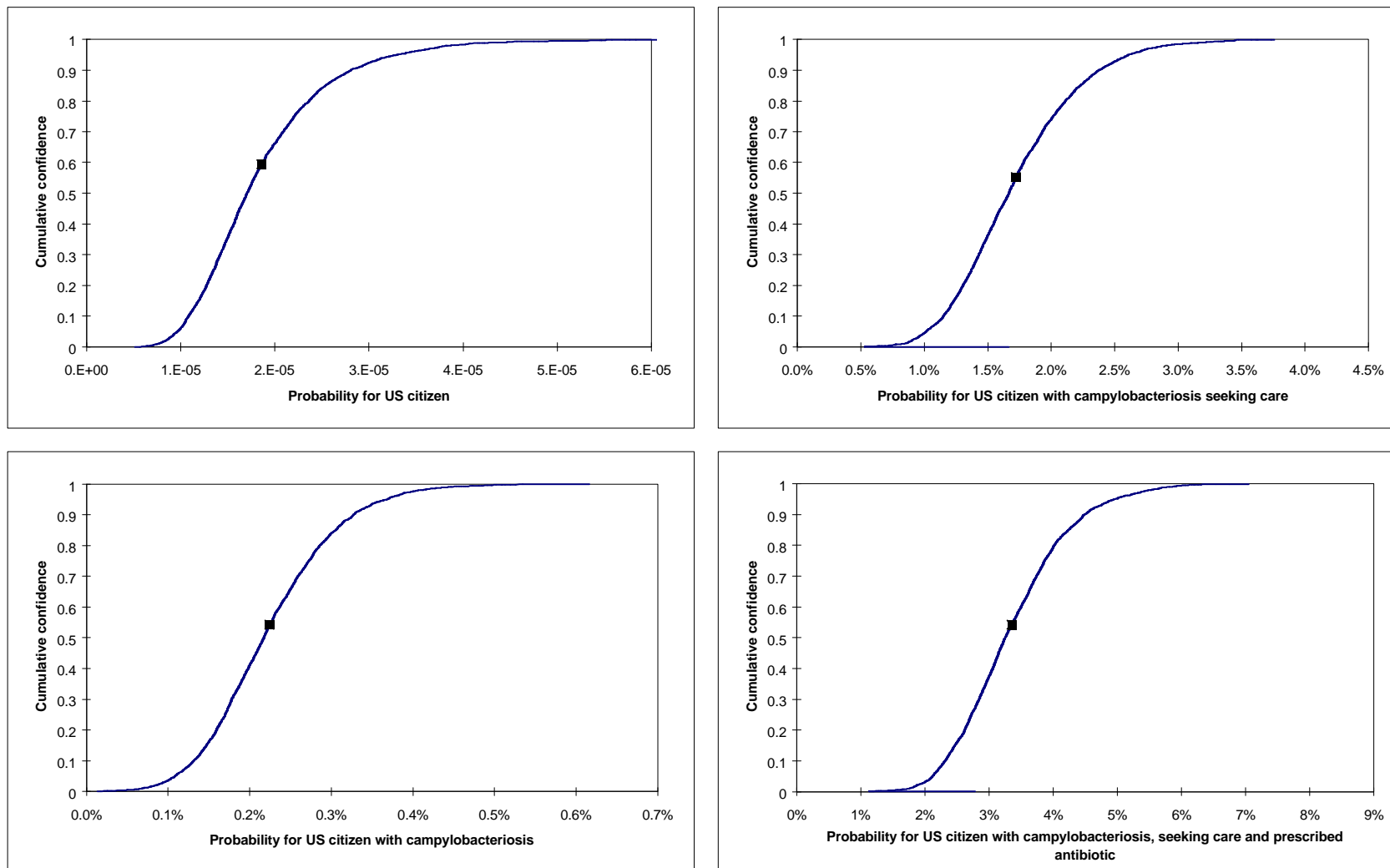
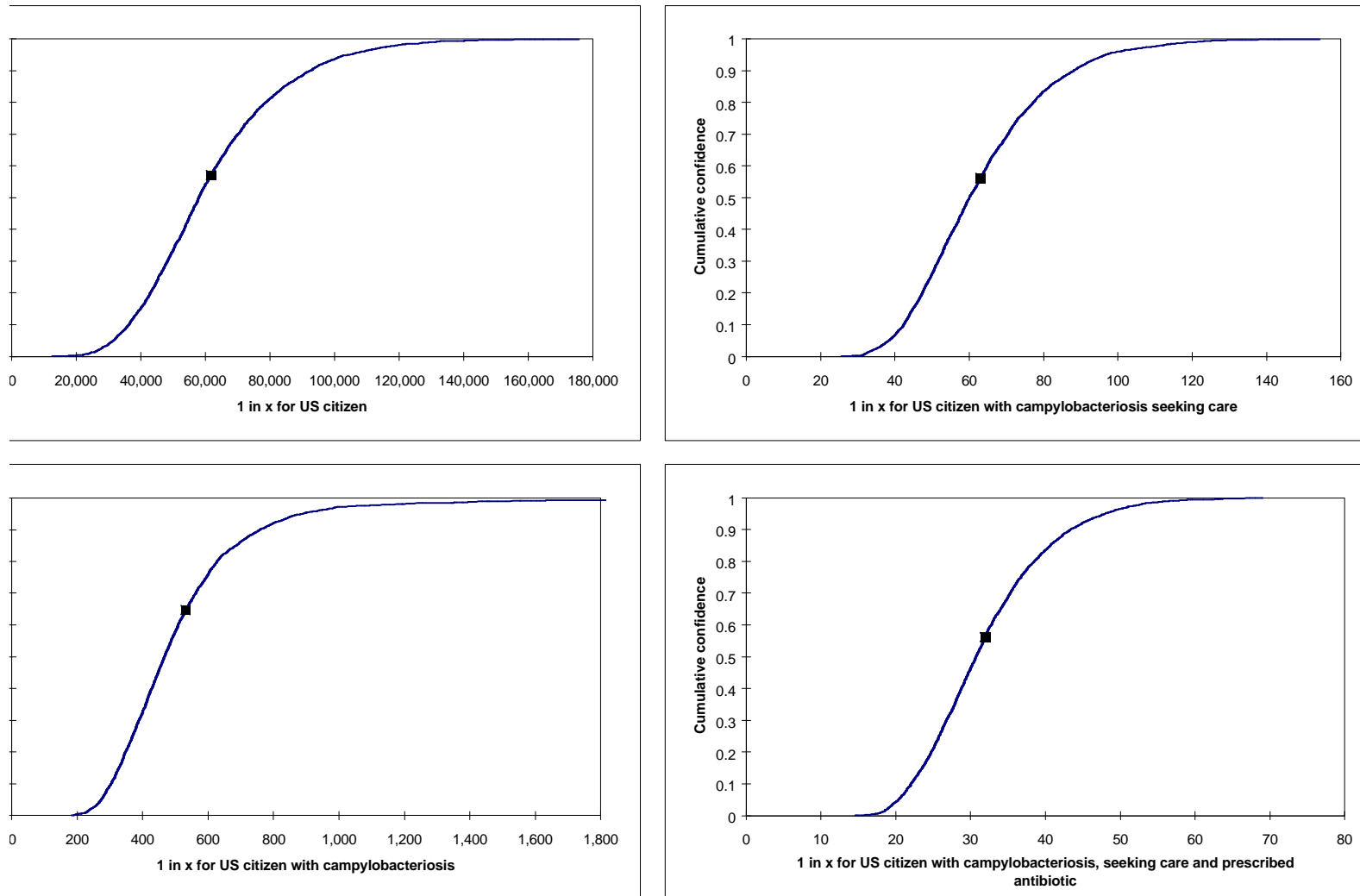
Figure 5.5a Confidence distributions for 1998 values for the probabilities described in this section for the four different denominators.

Figure 5.5b Confidence distributions for 1998 values for the probabilities described in this section (in 1 in x format) for the four different denominators



2. Number of cases

The level of human health burden may alternatively be measured simply as the number of people who contract fluoroquinolone resistant campylobacteriosis in a year where the *Campylobacter* is associated with domestically reared broilers (N3_T).

3. Incremental days of illness

A third option is to measure the human health impact as the number of extra people-days of illness that occur as a result of fluoroquinolone resistant *Campylobacter* associated with domestically reared broilers. This would potentially recognize that those people with invasive infection would have a much larger incremental duration of illness than those with enteric infection. However, problems arise in the definition of illness. In addition, there is no substantial evidence to suggest that people with enteric infection and bloody diarrhea will be ill longer than those with enteric infection and non-bloody diarrhea. Since some 99.6% of estimated cases of campylobacteriosis are enteric infections, calculating the number of incremental days of illness would amount to multiplying the number of enteric infections by some constant factor which was a difference of two medians, equivalent to a 3 day difference (71) or a mean difference of 2 days in the CDC Campylobacter Case Control Study (97).

There is some suggestion that fluoroquinolone –resistant *Campylobacter* may induce more severe or longer illness than susceptible strains. If this were found to be correct, incremental days of illness would become a more realistic measure of the human health impact.

Defining risk and strategies for controlling the risk

To ensure that this model can be used effectively to protect the public health, risk managers must determine the level of risk that expresses a quantitative definition of acceptable risk. In the past, these types of definitions have been established through public notice and comment rule making.

Once a quantitative definition of acceptable risk is established, the next step is to determine the harm or human health impact. In the Framework document, the Agency defined the potential human health impact associated with the use of an antimicrobial drug in food producing animals as the loss of effective drugs to treat human disease. The agency considered that evaluation would be made of the availability of effective alternative therapies to treat a particular disease. This risk assessment model looks at the use of an empiric therapy, fluoroquinolones to treat a food borne disease, and does not explicitly consider the issue of effective alternative therapies. However, as a regulatory tool, we can use the risk assessment approach to consider harm several different ways. The risk assessment can define the harm associated with acquiring a resistant food borne as: 1) having a resistant infection; 2) having a resistant infection and receiving the antibiotic; 3) having the resistant infection, receiving the antibiotic and experiencing an adverse effect, such as a change in duration of illness; or 4) having the resistant infection, receiving the antibiotic and having no alternative drug to treat the infection. The last approach is most consistent with the definition articulated in the Framework document.

The final risk management decision is to define the target population(s) that need protection. The measure of risk changes from 1 in 61,093 to 1 in 32 depending on whether the denominator is the total US population or persons with campylobacteriosis seeking care and prescribed an antibiotic (Table 5.1).

The probability column of Table 5.1 gives an estimate of the probability that an individual will experience an effect associated with resistant campylobacteriosis. The current standard used by the FDA for food additives, including new animal drug residues, focuses on protecting the 90th percentile consumer.

Recently, however, there has been increased interest and Congressional mandates to protect subpopulations such as children.

Defining a risk standard for assessing the microbial safety of new animal drugs

In the Framework Document, the Agency identified its goal as protecting the public health by ensuring that significant human antimicrobial therapies are not lost due to use of antimicrobials in food-producing animals, while providing for the safe use of antimicrobials in food-producing animals. Consistent with this goal, the Framework Document set out a categorization system for evaluating the microbial safety of antimicrobial drugs intended for use in food producing animals. In this document, the agency defined the potential human health impact associated with the use of an antimicrobial drug in food producing animals as the loss of effective drugs to treat human disease. The agency considered that evaluation would be made of the availability of effective alternative therapies to treat a particular disease.

Section 512 of the Federal Food, Drug, and Cosmetic Act, which establishes the conditions for approval of new animal drugs, requires that they be proven to be "safe." Even though section 201(u) of the Act provides that the use of the term "safe" in section 512 has reference to the health of man or animal, the term "safe" is not defined in section 512. Section 512 does require that determinations of safety include consideration of the probable consumption of the new animal drug and of any substance formed in or on food because of the use of the drug. Prior to the addition of section 512 to the Act by the Animal Drug Amendments of 1968, animal drugs were regulated under several sections of the Act. Substances formed in or on food due to the use of animal drugs were regulated under the food additive provisions in section 409 of the Act. Under section 409, such substances had to be shown to be safe. The term "safe" also is not defined in section 409 of the Act. Its legislative history, however, states, "safety requires proof of a reasonable certainty that no harm will result from the proposed use of the additive." H. Rept. No. 2284, 85th Cong., 2d. Sess. 4-5 (1958). The Animal Drug Amendments of 1968 merely consolidated all of the existing statutory authorities related to animal drugs into section 512 and the legislative history indicated that the consolidation in no way changed the authorities with respect to the regulation of new animal drugs. S. Rept. No. 1308, 90th Cong., 2d. Sess. 1 (1968).

While not appearing in the statute, a definition of "safe" or "safety" in the context of food additives has been established by regulation (21 CFR 570.3(i)), which states:

"Safe or safety means that there is a reasonable certainty in the minds of competent scientists that the substance is not harmful under the intended conditions of use. It is impossible in the present state of scientific knowledge to establish with complete certainty the absolute harmlessness of the use of any substance. Safety may be determined by scientific procedures or by general recognition of safety. In determining safety, the following factors shall be considered:

- (1) The probable consumption of the substance and of any substance formed in or on food because of its use.
- (2) The cumulative effect of the substance in the diet, taking into account any chemically or pharmacologically related substance or substances in such diet.
- (3) Safety factors which, in the opinion of experts..., are generally recognized as appropriate."

Therefore, the Agency routinely applies the "reasonable certainty of no harm" standard in determining the safety of substances formed in or on food as a result of the use of a new animal drug.

In applying that standard to new animal drug residues, the food safety assessments focus on identifying the hazard of the chemical to humans and controlling or limiting the exposure to the chemical. The hazard to humans is assessed by conducting a standard battery of toxicology tests in animals. These tests

are designed to determine the dose that causes the adverse effect and the dose at which no drug effect is seen, i.e., the no observed effect level (NOEL).

The NOEL of the most sensitive effect from the most sensitive toxicology study is divided by a safety factor to determine an acceptable daily intake (ADI). A safety factor of 1000, the product of three factors, is generally applied to animal studies of 90-day duration. One 10-fold factor is used to account for the uncertainty in extrapolating from animals to man. A second 10-fold factor is used to account for the variability among individuals and an additional 10-fold factor is used to extrapolate to a lifetime of exposure. The recent Food Quality Protection Act directed the EPA to impose an additional 10-fold safety factor for pesticides that are present in the diet of children. The amount of pesticide, food additive or drug residue permitted in the tissues of each edible commodity is based upon the quantity of food consumed daily by the 90th percentile consumer. For carcinogenic compounds used in food-producing animals, the agency allows an incremental risk of 1 in one million.

It is clear, however, that there is a significant difference between this traditional chemical residue-based determination of the safety of new animal drugs intended for food animal use and the determination of safety in the context of antimicrobial resistance. The former involves assessment of the risk of consumption of a chemical substance formed in or on food, i.e., residues of the new animal drug--which risk is not anticipated to change appreciably over time, while the latter involves assessment of the risk of a "substance", i.e., resistant microbes, which will not be present in food as an immediate consequence of approval, but which may appear with increasing prevalence over time as the animal drug is used.

The Framework document acknowledges and attempts to provide a mechanism to deal with this non-traditional risk by establishing that the risk to be assessed is the potential loss of effective therapy for human microbial disease. It provides for assessment of this risk through an initial categorization process involving an assessment of the importance of various drugs or drug classes to the treatment of microbial disease in humans coupled with an estimation of the potential for exposure of humans to resistant microorganisms derived from animals. Depending on the initial categorization, it continues the assessment via pre-approval studies intended to elucidate both the potential for particular drugs to select for resistant bacteria in animals and the rate at which such selection might take place. It also contemplates the establishment of resistance and monitoring thresholds (via formal quantitative risk assessment or otherwise) against which the continued safety of the animal drug will be assessed post-approval and with respect to which mitigation efforts may ensue, up to the point of drug withdrawal if all else fails.

All of this is intended to adequately protect the public health while permitting the approval of drugs to protect animal health. Implicit in the Framework document is the application of the safety standard in a manner which permits the implementation of the system proposed in this document to assure that the public health is protected by preserving the long-term effectiveness of antimicrobial drugs for treating diseases of humans. Therefore, in the context of the Framework document, requiring reasonable certainty that the public health will be protected as a condition of new animal drug approval (and subsequent use of the approved drug) does not necessarily equate to reasonable certainty that no individual will suffer any effect. Ensuring public health protection under the process proposed by the Framework document does require mechanisms to rapidly and effectively react to the results of post-approval monitoring, including one or more mechanisms to rapidly remove animal drugs from the market if the final safety threshold--the one which represents unacceptable risk to the public health--is exceeded.

Establishing Regulatory Thresholds

Once the risk standard is defined, the population of interest determined and the regulatory endpoint decided upon, this model might serve as a tool for establishing regulatory thresholds, a concept introduced in the Framework document. The FDA proposed to establish thresholds for the development of resistant bacteria in order to protect human health. There are two methods for establishing regulatory thresholds, technology-based and health-based. Technology-based thresholds are established by measuring the

amount of contaminant currently present. For example, HACCP limits for *Salmonella* contamination on carcasses were established by measuring the current level of carcass contamination. If a qualitative risk assessment suggests that this amount represents an unacceptable risk then further regulatory action is taken. In the HACCP regulation, USDA concluded that the current food borne disease burden due to *Salmonella* was too high and required the levels on carcasses be lowered.

A more detailed quantitative assessment can be conducted to determine the magnitude of the risk or if strategies can be developed to decrease the amount of contamination or to prevent or control the development of resistance. For antimicrobial resistance in animal food borne pathogens, a threshold could be established by measuring the amount of resistance present in the food borne pathogen for approved products or the amount projected to develop based on pre-approval studies. If this level represents an unacceptable public health risk, strategies can be developed to decrease the disease burden or resistance level. While technology-based thresholds have an advantage in ease of establishment, these values are not necessarily tied to public health outcomes.

Health-based thresholds are established based upon a quantitative risk or safety assessment. Since public health risk is a product of hazard times exposure, health-based thresholds are generally established by performing a comprehensive evaluation of both the hazard and exposure. Establishing health-based thresholds, however, is difficult and resource intensive due to the lack of quantitative data on public health outcomes related to the use of antimicrobials in food animals. Also, because of the uncertainty and quality of the data, some authors believe that health-based thresholds cannot be directly related to public health outcomes.

One approach would be to use a hybrid of the risk assessment approach and the safety factor approach to establish regulatory thresholds. For example, the complete risk assessment would be conducted for the pathogen that develops resistance the soonest (sentinel food borne pathogen) in the animal species associated with the most food borne disease due to that pathogen (the reference animal species). The model could then be used to determine when an unacceptable human health impact is reached (the resistance threshold); and to calculate the level of resistance permissible in the bacteria on the reference animal species at slaughter (monitoring threshold). This monitoring threshold could then be applied to all other species and be protective of the public health because the food borne disease burden from other species will be less than that in the reference species. For food borne pathogens with health impacts greater than that of the sentinel bacteria, it may not be possible to wait until resistance develops to assess the public health impact. In this case, a safety factor could be determined and applied to the monitoring threshold established for the sentinel bacteria to be protective of the public health. Mitigation action would be warranted when monitoring thresholds in either the sentinel or other food borne pathogens would be reached.

The agency believes that management of risk should be an ongoing process and not be initiated only when a monitoring threshold is reached. Comments at the Veterinary Medicine Advisory Committee in January 1999 and comments made to the Framework document docket expressed the need to implement judicious use principles in the selection and use of antimicrobial drugs in food-producing animals. The application of these principles are critical in managing the risk of antimicrobial resistance by limiting the use of important human antimicrobials in food producing animals and thereby reducing the selection pressure for the development of resistance.

The Hazard Analysis Critical Control Points (HACCP) regulations being implemented by USDA/FSIS have reduced the incidence of bacteria isolated from carcasses at slaughter in the plants in which the regulations have been applied. While this risk assessment was appropriately designed to estimate risk to human health from resistant food borne pathogens associated with the use of antimicrobials in food-producing animals, the current apparent effect of the HACCP regulations is to reduce human exposure to *Campylobacter*, which should concurrently reduce illness in people. Therefore, this is another critical factor in the overall management of risk to the consumer.

Using the Model to Determine if the Threshold is being, or will be, Exceeded

This risk assessment estimates the human health impact arising from the observed fluoroquinolone-resistant *Campylobacter* prevalence in broiler carcasses. It effectively derives a ratio (given the label k and described below) between the number of affected people (N_{3T} in the model) and the volume of contaminated meat (V_i in the model). The model as it stands provides a quickly and continuously updateable method of estimating the current human health impact. There is considerable uncertainty in estimating the ratio k because of imperfect data, but further data and more years of monitoring would improve this estimate.

In use as a regulatory tool, it is necessary to be able to estimate the *future* human health impact, particularly if a rapid rise in resistance is observed or expected in poultry. The purpose of evaluating the ratio k is to determine a future human health impact given some new resistance prevalence in poultry carcasses. The product of this estimated prevalence with a forecast of the future poultry consumption level and the ratio k is equal to the expected number of affected people. If the acceptable threshold has been defined as a probability for some specific group, as discussed above, this number can be translated into the appropriate probability measure.

The parameter k relates the *current* propensity of a pound of fluoroquinolone-resistant *Campylobacter* contaminated poultry meat to cause human illness. It implicitly takes into account the variety of paths that a quantity of poultry meat may take, including being thrown away, being well-cooked, cross-contaminating some other food product, etc. Radical change in the system would make the value of k irrelevant, for example, irradiation of food or any other system that would reduce the average *Campylobacter* load in contaminated carcasses. However, approximate corrections can be made to k to take account of such effects.

Theory behind, and use of, the parameter k

If one selects an infected item of food at some point in the production of a food product (e.g. an infected carcass at the spin chiller of a production plant which will contain some random number of servings), there are any number of potential probabilistic pathways for which the consumption of this item will eventuate in the infection of one or more people. The paths are probabilistic because of the inherent randomness of the system, so there must be some (unknown) probability distributions of the number of people that could become infected, ill, etc. from an individual serving. The shape of this distribution cannot be known because of the myriad ways that a person can become affected as a result of the consumption of an infected serving. The persons affected need not even be direct consumers of the serving: for example, they can become affected through contact with others who have consumed the serving, from other food that has come into contact with the serving in question, or from pets who have consumed the product. The shape of the distribution is a result of any remaining processing of the item, the history of its handling during distribution, the current consumption and food handling behavior of the consuming population, as well as the distribution of pathogenic load among infected product and the dose-response relationships for the various segments of the consuming population.

In the case of chickens, the number of people infected by a food pathogen is orders of magnitude lower than the numbers of servings infected with that pathogen, so this distribution must have a mean k that is much smaller than 1 (Figure 5.6)¹. Moreover, the probability of infecting two people from a serving will intuitively be considerably less than the probability of infecting just one person.

¹ When k is much less than 1, the unknown parameter k can be interpreted as approximately equal to the probability that a random consumer will experience the human health impact by consuming 1lb of infected broiler meat, which essentially takes the role of the more traditional dose-response model, excepting that one has implicitly included some cross-contamination, cross-infection, variations in pathogenic load among infected servings and variation in organism-host interaction.

Applying the conditional probability identity principle to this problem, we can write:

$$I = knp \quad (1)$$

where:

I is the mean number of people per year who will experience some human health effect as a result of consuming a pound of fluoroquinolone resistant *Campylobacter* contaminated broiler meat;
 n is the quantity (lbs.) of broiler meat consumed in a year in the US; and
 p is the prevalence of the fluoroquinolone resistant *Campylobacter* in the meat.

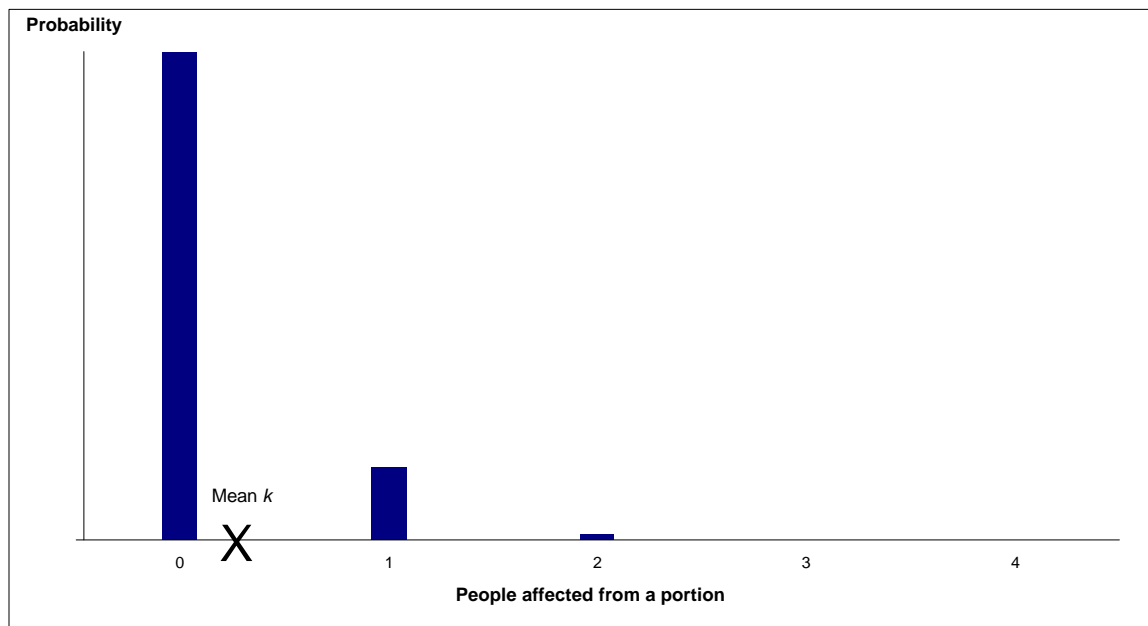


Figure 5.6: Probability distribution of number of affected people as a result of consuming one infected portion

Just as with the microbial pathogenicity approach to dose-response modeling using dose-response equations, the model parameter needs to be determined from data. In essence, this requires estimating the quantity of infected broiler meat consumed by the public in some recent time interval and estimating what I must have been, given the number of people experiencing the human health impacts of interest as a result of consuming those infected servings. In the model presented here, these two quantities for 1998 are represented by the model outputs V_i and $N3_T$.

Equation 1 can be put to practical use in determining the maximum acceptable prevalence (the “threshold prevalence”) of fluoroquinolone resistant *Campylobacter* infected broiler meat p_{max} as follows:

1. Determine unacceptable human health impact
2. Estimate values for k
3. Use the above equation to infer a p_{max} value for all bacteria in question.
4. Monitor broiler production and institute action when the first p_{max} is reached.

These steps are discussed more fully below.

1. Determining unacceptable human health impact

Determine some quantity that represents the threshold level of unacceptable human health impact. The number of human illnesses is governed by a sequence of stochastic processes and we cannot therefore determine, for a given risk level, the exact number of people who will become ill, etc. in any particular year. The threshold level of unacceptable human health impact could therefore be expressed in probabilistic terms, for example: “there is a 90% probability that no more than X people will become infected per year by fluoroquinolone resistant *Campylobacter* as a result of domestic consumption of domestically reared poultry”. Alternatively, the threshold level could be expressed as a probability like those calculated in Table 5.1, in which case the threshold would be expressed as, for example, ‘We are 90% confident that the risk of being affected is less than 1 in Y for a random U.S. citizen’. Although expressed differently to the previous example of a threshold definition, this second expression can be reworded in the same terms as the first definition.

2. Estimating values for k

Comparing the risk assessment model outputs with the parameters of Equation 1, we can write:

$$V_c * p_p * k = N3_T \quad (2)$$

or

$$V_i * k = N3_T$$

Rearranging for k :

$$k = N3_T / V_i$$

Hence, with uncertainty distributions for V_i and $N3_T$, we can determine a value with attendant uncertainty for k by a simple Monte Carlo simulation.

In using this analysis to predict future human health impact, we will need to assume further that:

1. The poultry consumption distribution patterns will remain constant, though the volumes may change;
2. Farming, slaughtering, processing, storing, retailing and consumer practices will not change markedly or, at least, without effect on the bacteria risk to the human population;
3. Human susceptibility remains constant during the period in which the fluoroquinolone resistant bacteria are monitored.

Where these assumptions prove to be inaccurate, corrections to the k values can and will need to be made. As more data becomes available the k values will become progressively better known. As more fluoroquinolone resistant *Campylobacter* infections occur, the assumptions of the model can be verified or otherwise.

3. Inferring a value for p_{max}

Assume that the threshold level of unacceptable human health impact has been determined: we should be $z\%$ sure that the human health impact will be no greater than t .

This equates to a maximum level of bacteria prevalence p_{max} in the broilers that needs to be determined, known in the framework document as the “resistance threshold”. This value can be determined empirically using Equation 2 by solving the following equation for p_{max} :

$$z = \iint \sum_0^t \frac{e^{-kV_c p_{max}} (kV_c p_{max})^x}{x!} f(k) f(V_c) dk dV_c$$

As more data becomes available, the uncertainty distribution for p_{max} will get narrower because the uncertainty for λ will get smaller. The agency would therefore be able to respond more appropriately in reassessing the maximum prevalence p_{max} as knowledge improves.

4. Using the model to manage the risk

The model determines the maximum prevalence p_{max} that can be allowed for fluoroquinolone resistant *Campylobacter* before reaching an unacceptable human health impact, given the current state of knowledge. It therefore only remains to monitor the *Campylobacter* prevalence to determine whether this threshold is being approached, or produce a forecast of prevalence to determine when p_{max} will be exceeded. The prevalence must be measured at the same place as used to determine p , i.e. at the slaughterhouses in this discussion.

The model discussed here can be improved by continuously collecting data on fluoroquinolone resistant and susceptible *Campylobacter* human health impacts. This will have two benefits:

1. one can verify that the model is, within reason, working as it should (i.e. it is probabilistically predicting the observed infections)
2. knowledge of the value for k will improve with more data, which can result in a reevaluation of the resistance threshold value p_{max} .